REMARKS

Claims 17-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Examiner states that "the claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Examiner also states that the specification has merely mentioned that gabapentin is a neuroleptic agent as adjunctive therapy in the treatment of central nervous system conditions in mammalian subjects, such as partial seizures, epilepsy, faintness attacks, hypokinesis, pain associated with shingles, and cranial trauma.

The Examiner then indicates that the "specification falls short because [it does not include] data essential for how partial seizures, epilepsy, faintness attacks, hypokinesis, pain associated with shingles, and cranial trauma can be treated by means of administering gabapentin to a patient with the above CNS disorders". This is because the CNS disorders can be caused by many different factors: inherited genetic abnormalities, problems in the immune system, injury to the brain or nervous system, diabetes, neuro-chemical imbalance (neurotransmitters), and etc."

Interestingly, the Examiner then states, "the state of the prior art is that according to Drugs of Future (vol. 9 no. 6, 1984p. 418-419), US Patent Nos. 5,095,148, 4,024,175, 4,152,326, and 5,132,451, gabapentin has been used as an anticonvulsant to treat a patient. US Patent No. 5,068,413 describes that it is useful in a therapy of certain cerebral disorders such as faintness attacks, hypokinesis and cranial traumas. Bennett et al. (J Clin psychopharmacol. 1997, Arr., 17(2):141-2) discloses gabapentin for treatment of bipolar and schizoaffective disorders. Bozikas et al. (Prog Neuropsychopharmacol Biol Psychiatry, 2002 Jan. 26 (1): 197-9) teaches

treatment of alcohol withdrawal with gabapentin. And Brannon et al. (Can J Psychiarty, 200 Feb; 45(1):84) has indicated that gabapentin can be used for treating post-traumatic stress disorder.

After discussing the prior art as disclosing all the indications mentioned by Applicants, the Examiner then inexplicably concludes that "there is no conclusive indicator that gabapentin can be used for treating all the CNS diseases such as partial seizures, epilepsy, faintness attaches, hypokinesis, pain associated with shingles, and cranial trauma except some of them."

By acknowledging that the prior art discloses the use of gabapentin, as an anticonvulsant to treat a patient, that it is useful in therapy of certain cerebral disorders such as faintness attacks, hypokinesis and cranial trauma, and for the treatment of bipolar and schizoaffective disorders, and for treating post-traumatic stress disorder, as disclosed in the above prior art references, Applicants fail to understand how the Examiner can then state that there is no conclusive indicator that gabapentin can be used for treating partial seizures, epilepsy, faintness attacks, hypokinesis, pain associated with shingles, and cranial trauma. More specifically, U.S. Pat. No. 4,087,544 having an issue date of May 2, 1978 claims and sets forth details on the treatment of "certain forms of epilepsy, faintness attacks, hypokinesia and cranial traumas." This patent is a divisional of U.S. Pat. No. 4,024,175 cited by the Examiner.

Applicants submit that the above prior art references listed by Examiner clearly establish the use of gabapentin to treat the claimed disorders is known. It is further noted that the FDA first approved gabapentin on December 30, 1993 for adjunctive therapy in the treatment of partial seizures associated with epilepsy. (See Electronic Orange Book, Approved Drug Products for Gabapentin and Physicians Desk Reference, 58th Edition, 2004, Neurontin

(gabapentin) Indications and Usage, p. 2559 – 2561, submitted herewith as Appendix I). Taken together, these references provide one of ordinary skill in the art with the requisite guidance to be able to prepare solid dose compositions of gabapentin tannate for the treatment of the CNS diseases identified in claims 17-19. Thus, the Examiner has failed to establish a *prima facie* case of nonenablement and the rejection of claims 17-19 based on 35 USC 112, first paragraph, should be withdrawn.

Applicants also note the Examiner's rejection of claims 1-19 under 35 U.S.C. 112, first paragraph, of August 8, 2006, was based on the use of the language "treating all the conditions of the central nervous system". The Examiner acknowledged then that the "State of the Prior Art" was the same as that identified above in the paragraph bridging pages 2 and 3.

The Examiner stated in the August 8, 2006 Non-final Rejection that there was no conclusive indicator that gabapentin can be used for treating all the CNS diseases except some of CNS diseases (emphasis added). This essentially is an acquiescence by the Examiner that he found enabling support for the CNS conditions disclosed in the prior art, but not for all CNS conditions.

Based on the above rejection, Applicants believed that the Examiner was rejecting claims 1-19 based on the language relating to the treatment of "all CNS disorders" and that the prior art identified by the Examiner offered sufficient guidance to one having ordinary skill in the art to enable one to treat certain conditions of the central nervous system including "partial seizures, epilepsy, faintness attacks, hypokinesis, pain associated with shingles and cranial trauma. Applicants amended claims 1-19 accordingly in the Amendment and Remarks submitted November 13, 2006.

In the Non-final Rejection of claims 1-19 mailed February 9, 2007, the Examiner rejected claims 1-19 provisionally on the ground of nonstatutory obviousness-type double patenting based on co-pending applications 10/806,260 and 10/806,022.

There was no mention of Applicants' Amendment and Remarks filed November 13, 2006 in response to the 35 U.S.C. 112 rejection, first paragraph, and there was no reiteration of a 112 rejection, first paragraph, with regard to claims 1-19. Applicants could only assume that the Amendment and Remarks of November 13, 2006 overcame the rejection mailed August 8, 2006. When a final or subsequent Office Action does not mention rejections or objections that were specified in an earlier Office Action, the assumption is that the Examiner has withdrawn the rejections. Accordingly, Applicants submitted two terminal disclaimers with regard to pending application numbers 10/806,260 and 10/806,022, thus expecting to receive a Notice of Allowance.

In the interim, Applicants filed an Information Disclosure Statement (IDS) June 12, 2007 to comply with Applicants' duty of disclosure identifying two references (*Chen et al.*, U.S. Pat. No. 6,383,471 and *Kiel et al.*, 2003/0077321A1) that had been overcome in co-pending patent application 10/806,022.

Surprisingly, another Non-final Rejection was mailed September 20, 2007, again rejecting claims 17-19 based on 35 U.S.C. 112, first paragraph, which Applicants believed had been allowed by the Examiner.

With regard to the Examiner's comment that the specification fails to provide working examples as to how the listed diseases can be treated with gabapentin, it is established case law that the specification need not contain a working example if the invention is otherwise disclosed in such manner that one skilled in the art would be able to practice the invention

without undue experimentation. In re Borkoski, 422 F2d 904, 164 USPQ 642, 645 (CCPA 1970.)

Based on the above, Applicants assert that the Examiner has failed to establish a *prima facie* case of lack of enablement and, based on the above prosecution history, is precluded from rejecting any of the claims pursuant to 35 U.S.C. 112, first paragraph. Accordingly, Applicants respectfully request that the rejection of claims 17-19 based on 35 U.S.C. 112, first paragraph, be withdrawn.

Claims 4-10 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 5-8, 11 of co-pending Application No. 10/269,027. Although the conflicting claims are not identical, it is argued that they are not patentably distinct from each other because the instant claim 1 is related to the process for preparing a gabapentin tannate pharmaceutical composition comprising mixing an anti-clumping agent, tannic acid together to form a reaction mixture; adding gabapentin to said reaction mixture; and adding one or more solvents to said reaction mixture, however, the instant invention differs from the co-pending Application No. in that the gabapentin tannate is not specified in claim 1.

Submitted herewith is a Terminal Disclaimer to overcome the double patenting rejection based on Application No. 10/269,029, now US Patent No. 7,273,623.

Claim Rejections – 35 U.S.C. § 103

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicants are advised of their obligation under 37 CFR 1.56 to point

out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a). Applicants advise that all inventors and invention dates of each claim were commonly owned at the time any inventions covered therein were made.

Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Patel et al.* (US Patent No. 6,248,363) in view of *Gordziel* (US Patent No. 6,037,358).

The Examiner indicates that *Patel et al.* disclose the general teachings of converting one of the active pharmaceutical ingredients (hydrophilic, amphiphilic or hydrophobic) such as gabapentin (see col. 5, line 46) into its tannate salt complex (see col. 40, line 7) as a salt of a pharmaceutically acceptable cation (see col.39, line 65).

Applicants assert that the *Patel et al.* reference is not relevant to the present application. The invention in the '363 patent is a solid pharmaceutical composition for a wide variety of pharmaceutical active ingredients combined with an effective solubilizing amount of a hydrophilic surfactant and a lipophilic additive so that the pharmaceutical active ingredient is either partially or fully solubilized.

Patel et al. has nothing to do with the formation of pharmaceutically active ingredients such as tannate salts. Gabapentin is listed as a 1 out of 68 preferred hydrophobic active ingredients. Gabapentin, by the way, is hydrophilic (see Merck Index in Appendix II), however, the '363 potential active ingredients also include hydrophilic ones. Tannic acid is merely listed as 1 of about 30 to 40 acids that can be used as a bufferant, see col. 39, lines 43 and 54, and col. 40, line 7. There is nothing in the '363 disclosure that even gives a reasonable

expectation that one of ordinary skill in the art would be able to prepare a gabapentin tannate salt.

The Examiner is factually incorrect when he states that *Patel et al.* expressly discloses that it seems reasonable to convert the active pharmaceutical ingredients such as chlorpheniramine (see col. 5, line 34) and gabapentin (see col. 5, line 46) into its tannate salt complex. *Patel et al.* discloses nothing at all with regard to the formation of chlorpheniramine or gabapentin tannate salts. *Patel et al.* offer a laundry list of many active ingredients which can be used with their hydrophilic and lipophilic surfactants to improve the solubility, stability, absorption and/or bioavailability of the pharmaceutical active ingredients. Tannic acid is listed merely as a bufferant.

With regard to *Gordziel*, the Examiner indicates that *Gordziel* discloses a process of preparing antihistamine tannates; for example, chlorpheniramine tannate can be obtained from reacting chlorpheniramine with tannic acid in the presence of isopropanol (see col. 1, lines 64-67).

Applicants agree. Significantly, however, the process set forth in *Gordziel* and the alternate routes mentioned in col. 2, lines 1 & 2, relate to the prepration of antihistamine tannates with no mention or suggestion of the preparation of gabapentin tannate.

Gordziel discloses the novel combination of phenylephrine tannate and chlorpheniramine tannate where MAS is used only as an excipient in the preparation of a suspension formulation. See Example 2.

The Examiner states that chlorpheniramine is equivalent to gabapentin for the purpose of preparing tannate salts. Attached as Appendix II are excerpts from The Merck Index, 13th Edition, 2001, p. 376 and 767 comparing the structures of chlorpheniramine with

gabapentin. As any chemist would appreciate, the two structures are not equivalent. Further, chlorpheniramine is an antihistamine and gabapentin is an anticonvulsant.

Claims 11-19 are rejected under 103(a) as being unpatentable over *Bryans et al.* (US Patent No. 7,141,606) in view of *Berge et al.* (J. of Pharm. Sciences, 66, No. 1, Jan, 1977, p. 1-19). The Examiner states that *Bryans et al.* expressly disclose gabapentin derivatives having a series of uses as set forth in col. 1, lines 22-26, and that gabapentin, as an amphoteric amino acid can form various salts as listed in col. 10, lines 33-37. But, as the Examiner states, the instant invention differs from *Bryans et al.* in that the formation of gabapentin tannate is not disclosed in the prior art.

The Examiner then states that *Berge et al.* describe potentially useful salts in the pharmaceutical compounds in which the salt is formed by an acid-base reaction involving either a proton-transfer or neutralization reaction (see page 2, left col., at the middle paragraph). Furthermore, the Examiner indicates that Table I shows various FDA-approved commercially marketed salts among which the tannate is displayed as one of the potential candidates for the pharmaceutical compounds.

With regard to *Berge et al.*, Table I lists approximately 70 FDA-approved commercially marketed salts including tannate. It is interesting to note that of all the salts in use through 1974, tannate salts represented only 0.88% usage. The *Berge et al.* reference does not disclose gabapentin as a potential compound to be modified. (See Table III).

Then the Examiner erroneously concludes that it would have been obvious to the skillful artisan in the art to be motivated to use the tannate for the salt of gabapentin for sleep disorders; this is because *Berge et al.* expressly teaches that one of the 70 FDA-approved commercially marketed salts can be the tannate.

Applicants respectfully traverse this rejection.

To establish a *prima facie* case of obviousness in light of the recent decision in KSR International Co. v. Telefax Inc. and Technology Holding Co., No. 04-1350, 119 Fed. Appx. 282 (2007), in addition to the four criteria set forth in Graham v. John Deere Co., 383 U.S. 1148 USPQ 459 (1966), the Examiner must determine "whether there was an apparent reason to combine" the prior art references to derive the claimed invention. The reason to make the claimed combination must be found in the prior art, and not based on Applicants' disclosure. Failure to show any of the foregoing negates a *prima facie* showing of obviousness.

The invention as defined in the claims is gabapentin tannate. It is the Examiner's position that one skilled in the art would be able to just pick the tannate salt of the claimed invention from the laundry list provided in the *Berge et al.* reference. This is unlikely because even *Berge et al.* state that "choosing the appropriate salt ... can be a very difficult task, since each salt imparts unique properties to the parent compound." (See page 1, col. 1, last sentence.) *Berge et al.* further state that "there is no reliable way of predicting the influence of a particular salt species on the behavior of the parent compound." (See page 1, col. 2, lines 7-9.) Furthermore, the Examiner fails to appreciate that the most commonly used salt in *Berge et al.* is hydrochloride at 42.98% usage compared to tannate at 0.88% usage. Consequently, Applicants assert that the *Berge et al.* reference teaches away from combining gabapentin with tannic acid to produce gabapentin tannate.

Merely identifying all of the elements of a claim or their equivalents in the prior art is not sufficient. Many inventions are combinations of old elements, and an Examiner may often find every element of a claimed invention in the prior art. If this finding were sufficient "to negate patentability, very few patents would ever issue." *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir.

1998). Therefore, in order to establish a *prima facia* rejection for obviousness, an "examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed." *In re Rouffet*, 149 F.3d 1350, 1357 (Fed.Cir. 1998).

Taking into consideration the following:

1) *Bryans et al.* disclose gabapentin (not gabapentin tannate) for treating insomnia. There is no mention of a tannate salt of gabapentin in *Bryans et al.*

2) *Berge et al.* disclose a laundry list of FDA approved salts including tannate at a usage of 0.88% compared to a usage of 42.98% for hydrochloride salts with no mention of gabapentin; and

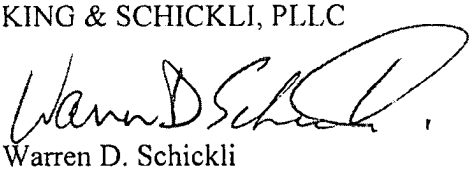
3) Applicants state in the present application that, while it is known that the formation of tannate salts with active pharmaceutical ingredients proceeds via a reaction of the amine groups or other basic functional groups of the active ingredient with the carboxylic or hydroxyl group present in tannic acid, in the gabapentin compound, the close proximity of a carboxylic acid group to the positively charged amine functional group was expected to prevent the formation of the tannate salt. (See page 4, first full paragraph of the present specification.)

4) Berge et al explicitly teaches that choosing the appropriate salt is a "very difficult task" and that "there is no reliable way of predicting the influence of a particular salt species on the behavior of the parent compound." Based upon these statements, Berge et al clearly does not provide a "reasonable expectation of success for the claimed combination." Under *In re Vaeck* 947 F2d 488, 20 USPQ2d 1438 (Fed. Cir 1991), a reasonable expectation of success must be found in the cited prior art, not the application.

Applicants request that, based on the above arguments, the rejection of claims 11-19 based on *Bryans et al.* and *Berge et al.* be withdrawn.

In summary, there is no reason alluded to in any of the cited references that would cause one of ordinary skill in the art to combine the references in the manner suggested by the Examiner. Accordingly, Applicants submit that claims 1-19 are patentable over the cited references and that claims 17-19 are enabled. Applicants believe that, based on the arguments submitted herewith and the enclosed terminal disclaimer, pending claims 1-19 are in condition for allowance and such action is respectfully requested.

Respectfully submitted,
KING & SCHICKLI, PLLC



Warren D. Schickli
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APPENDIX I

PDR®

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EDITION

2004

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ISBN: 1-56363-471-6

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PRODUCT INFORMATION

Endocrinologic—Hypernatremia.
Dermatologic—Pruritus, Skin rash, sweating.
Special Senses—Blurred vision, glaucoma.
Although reported less frequently, and sometimes only once, additional severe side effects include:
Nervous System—Ataxia, shock-like coma, toxic delirium, manic reaction, convulsions, acute anxiety reaction, precipitation of schizophrenia, transient respiratory and cardiovascular depression following ECT.
Gastrointestinal—To date, fatal progressive necrotizing intracellular damage has been reported in a very few patients. Reversible jaundice.
Hematologic—Leukopenia.
Immunologic—Lupus-like syndrome.
Metabolic—Hypermetabolic syndrome (which may include, but is not limited to, hyperpyrexia, tachycardia, tachypnea, muscular rigidity, elevated CK levels, metabolic acidosis, hypoxia, coma and may resemble an overdose).
Respiratory—Edema of the glottis.
Neural—Fever associated with increased muscle tone.
Withdrawal may be associated with nausea, vomiting, and malaise.
A common withdrawal syndrome following abrupt withdrawal of Nardil has been infrequently reported. Signs and symptoms of this syndrome generally commence 24 to 72 hours after drug discontinuation and may range from vivid dreams with agitation to frank psychosis and convulsions. This syndrome generally responds to reinstitution of low-dose Nardil therapy followed by cautious downward titration and discontinuation.

DOSAGE AND ADMINISTRATION

Initial dose: The usual starting dose of Nardil is one tablet (15 mg) three times a day.
Early phase treatment: Dosage should be increased to at least 60 mg per day at a fairly rapid pace consistent with patient tolerance. It may be necessary to increase dosage up to 90 mg per day to obtain sufficient MAO inhibition. Many patients do not show a clinical response until treatment at 90 mg has been continued for at least 4 weeks.
Maintenance dose: After maximum benefit from Nardil is achieved, dosage should be reduced slowly over several weeks. Maintenance dose may be as low as one tablet, 15 mg, a day or every other day, and should be continued for as long as is required.

OVERDOSAGE

Note—For management of *hypertensive crises* see WARNINGS section.
Accidental or intentional overdosage may be more common in patients who are depressed. It should be remembered that multiple drugs and/or alcohol may have been ingested.
Depending on the amount of overdosage with Nardil, a varying and mixed clinical picture may develop, including signs and symptoms of central nervous system and cardiovascular stimulation and/or depression. Signs and symptoms may be absent or minimal during the initial 12-hour period following ingestion and may develop slowly thereafter, reaching a maximum in 24–48 hours. Death has been reported following overdosage. Therefore, immediate hospitalization, with continuous patient observation and monitoring throughout this period, is essential.
Signs and symptoms of overdosage may include, alone or in combination, any of the following: drowsiness, dizziness, faintness, irritability, hyperactivity, agitation, severe headache, hallucinations, trismus, opisthotonus, rigidity, convulsions, and coma; rapid and irregular pulse, hypertension, hypotension, and vascular collapse; precordial pain, respiratory depression and failure, hyperpyrexia, diaphoresis, and cool, clammy skin.
Treatment: Intensive symptomatic and supportive treatment may be required. Induction of emesis or gastric lavage with instillation of charcoal slurry may be helpful in early poisoning, provided the airway has been protected against aspiration. Signs and symptoms of central nervous system stimulation, including convulsions, should be treated with diazepam, given slowly intravenously. Phenothiazine derivatives and central nervous system stimulants should be avoided. Hypotension and vascular collapse should be treated with intravenous fluids and, if necessary, blood pressure titration with an intravenous infusion of dilute pressor agent. It should be noted that adrenergic agents may produce a markedly increased pressor response.
Respiration should be supported by appropriate measures, including management of the airway, use of supplemental oxygen, and mechanical ventilatory assistance, as required.
Body temperature should be monitored closely. Intensive management of hyperpyrexia may be required. Maintenance of fluid and electrolyte balance is essential.
There are no data on the lethal dose in man. The pathophysiologic effects of massive overdosage may persist for several days, since the drug acts by inhibiting physiologic enzyme systems. With symptomatic and supportive measures, recovery from *mild* overdosage may be expected within 3 to 4 days.
Hemodialysis, peritoneal dialysis, and charcoal hemoperfusion may be of value in massive overdosage, but sufficient data are not available to recommend their routine use in these cases.
Toxic blood levels of phenelzine have not been established, and assay methods are not practical for clinical or toxicological use.

HOW SUPPLIED

Each Nardil tablet is orange, biconvex, glossy sugar-coated, and imprinted with "P-D 270" in brown ink and contains phenelzine sulfate equivalent to 15 mg of phenelzine base.
N 0071-0270-24 Bottles of 100
Storage: Store between 15°–30° C (59°–85°F).
Rx only
US Patent 3,314,855
Revised August 1998 0270C081
Shown in Product Identification Guide, page 330

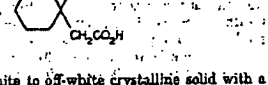
NEURONTIN® ℞
(gabapentin) Capsules

NEURONTIN®
(gabapentin) Tablets

NEURONTIN®
(gabapentin) Oral Solution

DESCRIPTION

Neurontin® (gabapentin) Capsules, Neurontin® (gabapentin) Tablets, and Neurontin® (gabapentin) Oral Solution are supplied as imprinted hard shell capsules containing 100 mg, 300 mg, and 400 mg of gabapentin, elliptical film-coated tablets containing 600 mg and 800 mg of gabapentin or an oral solution containing 250 mg/5 mL of gabapentin.
The inactive ingredients for the capsules are lactose, cornstarch, and talc. The 100 mg capsule shell contains gelatin and titanium dioxide. The 300 mg capsule shell contains gelatin, titanium dioxide, and yellow iron oxide. The 400 mg capsule shell contains gelatin, red iron oxide, titanium dioxide, and yellow iron oxide. The imprinting ink contains FD&C Blue No. 2 and titanium dioxide.
The inactive ingredients for the tablets are poloxamer 407, copovidone, cornstarch, magnesium stearate, hydroxypropyl cellulose, talc, candelilla wax and purified water. The imprinting ink for the 600 mg tablets contains synthetic black iron oxide, pharmaceutical shellac, pharmaceutical glaze, propylene glycol, ammonium hydroxide, isopropyl alcohol and n-butyl alcohol. The imprinting ink for the 800 mg tablets contains synthetic yellow iron oxide, synthetic red iron oxide, hydroxypropyl methylcellulose, propylene glycol, methanol, isopropyl alcohol and deionized water.
The inactive ingredients for the oral solution are glycerin, xylitol, purified water and artificial cool strawberry anise flavor.
Gabapentin is described as 1-(aminomethyl)cyclohexaneacetic acid with a molecular formula of $C_9H_{17}NO_2$ and a molecular weight of 171.24. The structural formula of gabapentin is:



Gabapentin is a white to off-white crystalline solid with a pK_{a1} of 3.7 and a pK_{a2} of 10.7. It is freely soluble in water and both basic and acidic aqueous solutions. The log of the partition coefficient (n-octanol/0.05M phosphate buffer) at pH 7.4 is −1.25.

CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism by which gabapentin exerts its analgesic action is unknown, but in animal models of analgesia, gabapentin prevents allodynia (pain-related behavior in response to a normally innocuous stimulus) and hyperalgesia (exaggerated response to painful stimuli). In particular, gabapentin prevents pain-related responses in several models of neuropathic pain in rats or mice (e.g. spinal nerve ligation models, streptozocin-induced diabetes model, spinal cord injury model, acute herpes zoster infection model). Gabapentin also decreases pain-related responses after peripheral inflammation (carrageenan footpad test, late phase of formalin test). Gabapentin did not alter immediate pain-related behaviors (rat tail flick test, formalin footpad acute phase, acetic acid abdominal constriction test, footpad heat irradiation test). The relevance of these models to human pain is not known.
The mechanism by which gabapentin exerts its anticonvulsant action is unknown, but in animal test systems designed to detect anticonvulsant activity, gabapentin prevents seizures as do other marketed anticonvulsants. Gabapentin exhibits antiseizure activity in mice and rats in both the maximal electroshock and pentylenetetrazole seizure models and other preclinical models (e.g., strains with genetic epilepsy, etc.). The relevance of these models to human epilepsy is not known.
Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) but it does not modify $GABA_A$ or $GABA_B$ radioligand binding, it is not converted metabolically into GABA or a GABA agonist, and it is not an inhibitor of GABA uptake or degradation. Gabapentin was tested in radioligand binding assays at concentrations up to 100 μM and did not exhibit affinity for a number of other common receptor sites, including benzodiazepine, glutamate, N-methyl-D-aspartate (NMDA), quisqualate, kainate, strychnine-insensitive or strychnine-sensitive glycine, alpha 1, alpha 2, or beta adrenergic, adenosine A1 or A2, cholinergic muscarinic or nicotinic, dopamine D1 or D2, histamine H1, serotonin S1 or S2, opiate mu, delta or kappa, cannabinoid 1, voltage-sensitive calcium channel sites labeled with nitrendipine or diltiazem, or at voltage-sensitive sodium channel sites labeled with batrachotoxinin A 20-alpha-benzoate. Furthermore, gabapentin did not alter the cellular uptake of dopamine, noradrenaline, or serotonin.
In vitro studies with radiolabeled gabapentin have revealed a gabapentin binding site in areas of rat brain including neocortex and hippocampus. A high-affinity binding protein in animal brain tissue has been identified as an auxiliary subunit of voltage-activated calcium channels. However, functional correlates of gabapentin binding, if any, remain to be elucidated.

Pharmacokinetics and Drug Metabolism

All pharmacological actions following gabapentin administration are due to the activity of the parent compound; gabapentin is not appreciably metabolized in humans.
Oral Bioavailability: Gabapentin bioavailability is not dose proportional; i.e., as dose is increased, bioavailability decreases. Bioavailability of gabapentin is approximately 60%, 47%, 34%, 33%, and 27% following 900, 1200, 2400, 3600, and 4800 mg/day given in 3 divided doses, respectively. Food has only a slight effect on the rate and extent of absorption of gabapentin (14% increase in AUC and C_{max}).
Distribution: Less than 3% of gabapentin circulates bound to plasma protein. The apparent volume of distribution of gabapentin after 150 mg intravenous administration is 58±6 L (Mean ±SD). In patients with epilepsy, steady-state predose (C_{min}) concentrations of gabapentin in cerebrospinal fluid were approximately 20% of the corresponding plasma concentrations.
Elimination: Gabapentin is eliminated from the systemic circulation by renal excretion as unchanged drug. Gabapentin is not appreciably metabolized in humans.
Gabapentin elimination half-life is 5 to 7 hours and is unaltered by dose or following multiple dosing. Gabapentin elimination rate constant, plasma clearance, and renal clearance are directly proportional to creatinine clearance (see Special Populations: Patients With Renal Insufficiency, below). In elderly patients, and in patients with impaired renal function, gabapentin plasma clearance is reduced. Gabapentin can be removed from plasma by hemodialysis. Dosage adjustment in patients with compromised renal function or undergoing hemodialysis is recommended (see DOSAGE AND ADMINISTRATION, Table 5).
Special Populations: *Adult Patients With Renal Insufficiency:* Subjects (N=60) with renal insufficiency (mean creatinine clearance ranging from 13-114 mL/min) were administered single 400 mg oral doses of gabapentin. The mean gabapentin half-life ranged from about 6.5 hours (patients with creatinine clearance >60 mL/min) to 52 hours (creatinine clearance <30 mL/min) and gabapentin renal clearance from about 90 mL/min (>60 mL/min group) to about 10 mL/min (<30 mL/min). Mean plasma clearance (CL/F) decreased from approximately 190 mL/min to 20 mL/min.
Dosage adjustment in adult patients with compromised renal function is necessary (see DOSAGE AND ADMINISTRATION). Pediatric patients with renal insufficiency have not been studied.
Hemodialysis: In a study in anuric subjects (N=11), the apparent elimination half-life of gabapentin on nondialysis days was about 132 hours; during dialysis the apparent half-life of gabapentin was reduced to 3.8 hours. Hemodialysis thus has a significant effect on gabapentin elimination in anuric subjects.
Dosage adjustment in patients undergoing hemodialysis is necessary (see DOSAGE AND ADMINISTRATION).
Hepatic Disease: Because gabapentin is not metabolized, no study was performed in patients with hepatic impairment.
Age: The effect of age was studied in subjects 20-80 years of age. Apparent oral clearance (CL/F) of gabapentin decreased as age increased, from about 225 mL/min in those under 30 years of age to about 125 mL/min in those over 70 years of age. Renal clearance (CLr) and CLr adjusted for body surface area also declined with age; however, the decline in the renal clearance of gabapentin with age can largely be explained by the decline in renal function. Reduction of gabapentin dose may be required in patients who have age related compromised renal function. (See PRECAUTIONS, Geriatric Use, and DOSAGE AND ADMINISTRATION.)
Pediatric: Gabapentin pharmacokinetics were determined in 48 pediatric subjects between the ages of 1 month and 12 years following a dose of approximately 10 mg/kg. Peak plasma concentrations were similar across the entire age group and occurred 2 to 3 hours postdose. In general, pediatric subjects between 1 month and <5 years of age achieved approximately 30% lower exposure (AUC) than that observed in those 5 years of age and older. Accordingly, oral clearance normalized per body weight was higher in the younger children. Apparent oral clearance of gabapentin

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Neurontin—Cont.

was directly proportional to creatinine clearance. Gabapentin elimination half-life averaged 4.7 hours and was similar across the age groups studied.

A population pharmacokinetic analysis was performed in 253 pediatric subjects between 1 month and 13 years of age. Patients received 10 to 65 mg/kg/day given TID. Apparent oral clearance (CL/F) was directly proportional to creatinine clearance and this relationship was similar following a single dose and at steady state. Higher oral clearance values were observed in children <5 years of age compared to those observed in children 5 years of age and older, when normalized per body weight. The clearance was highly variable in infants <1 year of age. The normalized CL/F values observed in pediatric patients 5 years of age and older were consistent with values observed in adults after a single dose. The oral volume of distribution normalized per body weight was constant across the age range.

These pharmacokinetic data indicate that the effective daily dose in pediatric patients with epilepsy ages 3 and 4 years should be 40 mg/kg/day to achieve average plasma concentrations similar to those achieved in patients 5 years of age and older receiving gabapentin at 30 mg/kg/day. (See DOSAGE AND ADMINISTRATION).

Gender: Although no formal study has been conducted to compare the pharmacokinetics of gabapentin in men and women, it appears that the pharmacokinetic parameters for males and females are similar and there are no significant gender differences.

Race: Pharmacokinetic differences due to race have not been studied. Because gabapentin is primarily renally excreted and there are no important racial differences in creatinine clearance, pharmacokinetic differences due to race are not expected.

Clinical Studies

Postherpetic Neuralgia:

Neurontin® was evaluated for the management of postherpetic neuralgia (PHN) in 2 randomized, double-blind, placebo-controlled, multicenter studies; N=563 patients in the intent-to-treat (ITT) population (Table 1). Patients were enrolled if they continued to have pain for more than 3 months after healing of the herpes zoster skin rash.

(See table 1 above)

Each study included a 1-week baseline during which patients were screened for eligibility and a 7- or 8-week double-blind phase (3 or 4 weeks of titration and 4 weeks of fixed dose). Patients initiated treatment with titration to a maximum of 900 mg/day gabapentin over 3 days. Dosages were then to be titrated in 600 to 1200 mg/day increments at 3- to 7-day intervals to target dose over 3 to 4 weeks. In Study 1, patients were continued on lower doses if not able to achieve the target dose. During baseline and treatment, patients recorded their pain in a daily diary using an 11-point numeric pain rating scale ranging from 0 (no pain) to 10 (worst possible pain). A mean pain score during baseline of at least 4 was required for randomization (baseline mean pain score for Studies 1 and 2 combined was 6.4). Analyses were conducted using the ITT population (all randomized patients who received at least one dose of study medication). Both studies showed significant differences from placebo at all doses tested.

A significant reduction in weekly mean pain scores was seen by Week 1 in both studies, and significant differences were maintained to the end of treatment. Comparable treatment effects were observed in all active treatment arms. Pharmacokinetic/pharmacodynamic modeling provided confirmatory evidence of efficacy across all doses. Figures 1 and 2 show these changes for Studies 1 and 2.

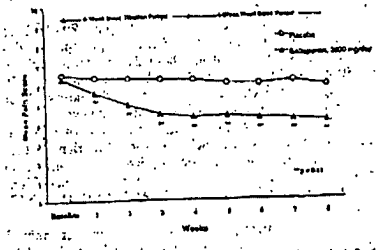

Figure 1. Weekly Mean Pain Scores (Observed Cases in ITT Population): Study 1

(See figure 2 at top of next column)

The proportion of responders (those patients reporting at least 50% improvement in endpoint pain score compared with baseline) was calculated for each study (Figure 3).

(See figure 3 at top of next column)

Epilepsy

The effectiveness of Neurontin® as adjunctive therapy (added to other antiepileptic drugs) was established in multicenter placebo-controlled, double-blind, parallel-group clinical trials in adult and pediatric patients (3 years and older) with refractory partial seizures.

Evidence of effectiveness was obtained in three trials conducted in 705 patients (age 12 years and above) and one trial conducted in 247 pediatric patients (3 to 12 years of age). The patients enrolled had a history of at least 4 partial seizures per month in spite of receiving one or more antiepileptic drugs at therapeutic levels and were observed on their established antiepileptic drug regimen during a 12-week baseline period (6 weeks in the study of pediatric patients). In patients continuing to have at least 2 (or 4 in some studies) seizures per month, Neurontin® or placebo was then added on to the existing therapy during a 12-week treatment period. Effectiveness was assessed primarily on the basis of the percent of patients with a 50% or greater reduction in seizure frequency from baseline to treatment (the "responder rate") and a derived measure called response ratio, a measure of change defined as (T - B)/(T + B), where B is the patient's baseline seizure frequency and T is the patient's seizure frequency during treatment. Response ratio is distributed within the range -1 to +1. A zero value indicates no change while complete elimination of seizures would give a value of -1; increased seizure rates would give positive values. A response ratio of -0.33 corresponds to a 50% reduction in seizure frequency. The results given below are for all partial seizures in the intent-to-treat (all patients who received any doses of treatment) population in each study, unless otherwise indicated.

Table 1. Controlled PHN Studies: Duration, Dosages, and Number of Patients

Study	Study Duration	Gabapentin (mg/day)[a] Target Dose	Patients Receiving Gabapentin	Patients Receiving Placebo
1	8 weeks	3600	113	116
2	7 weeks	1800, 2400	223	111
		Total	336	227

[a]Given in 3 divided doses (TID)

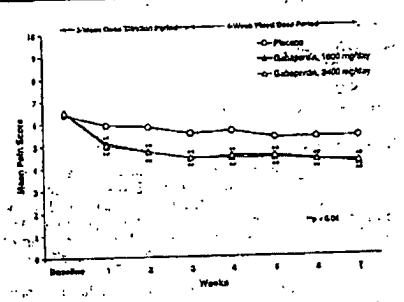

Figure 2. Weekly Mean Pain Scores (Observed Cases in ITT Population): Study 2

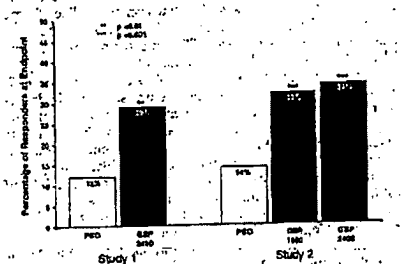

Figure 3. Proportion of Responders (patients with ≥50% reduction in pain score) in Endpoint-Controlled PHN Studies

One study compared Neurontin® 1200 mg/day divided TID with placebo. Responder rate was 29% (14/61) in the Neurontin® group and 9% (6/66) in the placebo group; the difference between groups was statistically significant. Response ratio was also better in the Neurontin® group (-0.199) than in the placebo group (-0.044), a difference that also achieved statistical significance.

A second study compared primarily 1200 mg/day divided TID Neurontin® (N=101) with placebo (N=98). Additional smaller Neurontin® dosage groups (600 mg/day, N=53; 1800 mg/day, N=54) were also studied for information regarding dose response. Responder rate was higher in the Neurontin® 1200 mg/day group (16%) than in the placebo group (8%), but the difference was not statistically significant. The responder rate at 600 mg (17%) was also not significantly higher than in the placebo, but the responder rate in the 1800 mg group (26%) was statistically significantly superior to the placebo rate. Response ratio was better in the Neurontin® 1200 mg/day group (-0.103) than in the placebo group (-0.022); but this difference was also not statistically significant ($p = 0.224$). A better response was seen in the Neurontin® 600 mg/day group (-0.105) and 1800 mg/day group (-0.222) than in the 1200 mg/day group, with the 1800 mg/day group achieving statistical significance compared to the placebo group.

A third study compared Neurontin® 900 mg/day divided TID (N=111) and placebo (N=109). An additional Neurontin® 1200 mg/day dosage group (N=52) provided dose-response data. A statistically significant difference in responder rate was seen in the Neurontin® 900 mg/day group (22%) compared to that in the placebo group (10%). Response ratio was also statistically significantly superior in the Neurontin® 900 mg/day group (-0.119) compared to that in the placebo group (-0.027), as was response ratio in 1200 mg/day Neurontin® (-0.184) compared to placebo.

Analyses were also performed in each study to examine the effect of Neurontin® on preventing secondarily generalized tonic-clonic seizures. Patients who experienced a secondarily generalized tonic-clonic seizure in either the baseline or in the treatment period in all three placebo-controlled studies were included in these analyses. There were significant response ratio comparisons that showed a statistically significant advantage for Neurontin® compared to placebo and favorable trends for almost all comparisons.

Analysis of responder rate using combined data from all three studies and all doses (N=152, Neurontin®, N=83; placebo, N=69) also showed a significant advantage for Neurontin® over placebo in reducing the frequency of secondarily generalized tonic-clonic seizures.

In two of the three controlled studies, more than one dose of Neurontin® was used. Within each study the results did not show a consistently increased response to dose. However, looking across studies, a trend toward increasing efficacy with increasing dose is evident (see Figure 4).

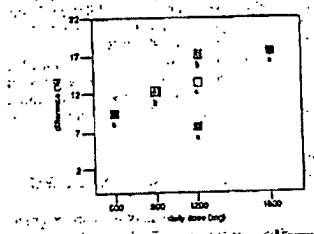

FIGURE 4: Responder Rate in Patients Receiving Neurontin® Expressed as a Difference from Placebo by Dose and Study

In the figure, treatment effect magnitude, measured on the Y axis in terms of the difference in the proportion of gabapentin and placebo assigned patients attaining a 50% or greater reduction in seizure frequency from baseline, is plotted against the daily dose of gabapentin administered (X axis).

Although no formal analysis by gender has been performed, estimates of response (Response Ratio) derived from controlled trials (398 men, 307 women) indicate no important gender differences exist. There was no consistent pattern in these data that age had any effect on the response to Neurontin®. There were insufficient numbers of patients of races other than Caucasian to permit a comparison of efficacy across racial groups.

A fourth study in pediatric patients age 3 to 12 years compared 25–35 mg/kg/day Neurontin® (N=118) with placebo (N=127). For all partial seizures in the intent-to-treat population, the response ratio was statistically significantly better for the Neurontin group (-0.146) than for the placebo group (-0.079). For the same population, the responder rate for Neurontin® (21%) was not significantly different from placebo (18%).

A study in pediatric patients age 1 month to 3 years compared 40 mg/kg/day Neurontin® (N=38) with placebo (N=38) in patients who were receiving at least one concomitant antiepileptic drug and had at least one partial seizure during the screening period (within 2 weeks prior to baseline). Patients had up to 48 hours of baseline and up to 48 hours of double-blind video EEG monitoring to record and count the occurrence of seizures. There were no statistically significant differences between treatments in either response ratio or responder rate.

INDICATIONS AND USAGE

Postherpetic Neuralgia

Neurontin® (gabapentin) is indicated for the management of postherpetic neuralgia in adults.

Epilepsy

Neurontin® (gabapentin) is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients over 12 years of age with epilepsy. Neurontin is also indicated as adjunctive therapy in the treatment of partial seizures in pediatric patients age 3–12 years.

CONTRAINDICATIONS

Neurontin® is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

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WARNINGS

Neuropsychiatric Adverse Events—Pediatric Patients 3-12 Years of age

Gabapentin use in pediatric patients with epilepsy 3–12 years of age is associated with the occurrence of central nervous system related adverse events. The most significant of these can be classified into the following categories: 1) emotional lability (primarily behavioral problems), 2) hostility, including aggressive behaviors, 3) thought disorder, including concentration problems and change in school performance, and 4) hyperkinesia (primarily restlessness and hyperactivity). Among the gabapentin-treated patients, most of the events were mild to moderate in intensity.

In controlled trials in pediatric patients 3–12 years of age the incidence of these adverse events was: emotional lability 2.4% (gabapentin-treated patients) vs 1.3% (placebo-treated patients); hostility 2.2% vs 1.3%; hyperkinesia 4.7% vs 2.5%; and thought disorder 1.7% vs 0%. One of these events, a report of hostility, was considered serious. Discontinuation of gabapentin treatment occurred in 1.3% of patients reporting emotional lability and hyperkinesia and 0.9% of gabapentin-treated patients reporting hostility and thought disorder. One placebo-treated patient (0.4%) withdrew due to emotional lability.

Withdrawal Precipitated Seizure, Status Epilepticus

Antiepileptic drugs should not be abruptly discontinued because of the possibility of increasing seizure frequency.

In the placebo-controlled studies in patients >12 years of age, the incidence of status epilepticus in patients receiving Neurontin® was 0.6% (3 of 543) versus 0.5% in patients receiving placebo (2 of 378). Among the 2074 patients >12 years of age treated with Neurontin® across all studies (controlled and uncontrolled) 31 (1.5%) had status epilepticus. Of these, 14 patients had no prior history of status epilepticus either before treatment or while on other medications. Because adequate historical data are not available, it is impossible to say whether or not treatment with Neurontin® is associated with a higher or lower rate of status epilepticus than would be expected to occur in a similar population not treated with Neurontin®.

Tumorigenic Potential

In a standard preclinical *in vivo* lifetime carcinogenicity studies, an unexpectedly high incidence of pancreatic acinar adenocarcinomas was identified in male, but not female, rats. (See PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility.) The clinical significance of this finding is unknown. Clinical experience during gabapentin's premarketing development provides no direct means to assess its potential for inducing tumors in humans.

In clinical studies in adjunctive therapy in epilepsy comprising 2085 patient-years of exposure in patients >12 years of age, new tumors were reported in 10 patients (2 breast, 3 brain, 2 lung, 1 adrenal, 1 non-Hodgkin's lymphoma, 1 endometrial carcinoma *in situ*), and preexisting tumors worsened in 11 patients (9 brain, 1 breast, 1 prostate) during or up to 2 years following discontinuation of Neurontin®. Without knowledge of the background incidence and recurrence in a similar population not treated with Neurontin®, it is impossible to know whether the incidence seen in this cohort is or is not affected by treatment.

Sudden and Unexplained Death in Patients With Epilepsy

During the course of premarketing development of Neurontin® 8 sudden and unexplained deaths were recorded among a cohort of 2203 patients treated (2103 patient-years of exposure).

One of these could represent seizure-related deaths in which the seizure was not observed, e.g., at night. This represents an incidence of 0.0038 deaths per patient-year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving Neurontin® (ranging from 0.0005 for the general population of epileptics to 0.003 for a clinical trial population similar to that in the Neurontin® program, to 0.005 for patients with refractory epilepsy). Consequently, whether these figures are reassuring or raise further concern depends on comparability of the populations reported upon to the Neurontin® cohort and the accuracy of the estimates provided.

PRECAUTIONS

Information for Patients

Patients should be instructed to take Neurontin® only as prescribed.

Patients should be advised that Neurontin® may cause dizziness, somnolence and other symptoms and signs of CNS depression. Accordingly, they should be advised neither to drive a car nor to operate other complex machinery until they have gained sufficient experience on Neurontin® to gauge whether or not it affects their mental and/or motor performance adversely.

Patients who require concomitant treatment with morphine may experience increases in gabapentin concentrations. Patients should be carefully observed for signs of CNS depression, such as somnolence, and the dose of Neurontin® or morphine should be reduced appropriately (see Drug Interactions).

Laboratory Tests

Clinical trials data do not indicate that routine monitoring of clinical laboratory parameters is necessary for the safe use of Neurontin®. The value of monitoring gabapentin blood concentrations has not been established. Neurontin® may be used in combination with other antiepileptic drugs without concern for alteration of the blood concentrations of gabapentin or of other antiepileptic drugs.

Drug Interactions

In vitro studies were conducted to investigate the potential of gabapentin to inhibit the major cytochrome P450 enzymes (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) that mediate drug and xenobiotic metabolism using isoform selective marker substrates and human liver microsomal preparations. Only at the highest concentration tested (171 μg/mL; 1 mM) was a slight degree of inhibition (14%-30%) of isoform CYP2A6 observed. No inhibition of any of the other isoforms tested was observed at gabapentin concentrations up to 171 μg/mL (approximately 15 times the C_{max} at 3600 mg/day).

Gabapentin is not appreciably metabolized nor does it interfere with the metabolism of commonly coadministered antiepileptic drugs.

The drug interaction data described in this section were obtained from studies involving healthy adults and adult patients with epilepsy.

Phenytoin: In a single (400 mg) and multiple dose (400 mg TID) study of Neurontin® in epileptic patients (N=8) maintained on phenytoin monotherapy for at least 2 months, gabapentin had no effect on the steady-state trough plasma concentrations of phenytoin and phenytoin had no effect on gabapentin pharmacokinetics.

Carbamazepine: Steady-state trough plasma carbamazepine and carbamazepine 10, 11 epoxide concentrations were not affected by concomitant gabapentin (400 mg TID; N=12) administration. Likewise, gabapentin pharmacokinetics were unaltered by carbamazepine administration.

Valproic Acid: The mean steady-state trough serum valproic acid concentrations prior to and during concomitant gabapentin administration (400 mg TID; N=17) were not different and neither were gabapentin pharmacokinetic parameters affected by valproic acid.

Phenobarbital: Estimates of steady-state pharmacokinetic parameters for phenobarbital or gabapentin (300 mg TID; N=12) are identical whether the drugs are administered alone or together.

Naproxen: Coadministration (N=18) of naproxen sodium capsules (250 mg) with Neurontin® (125 mg) appears to increase the amount of gabapentin absorbed by 12% to 15%. Gabapentin had no effect on naproxen pharmacokinetic parameters. These doses are lower than the therapeutic doses for both drugs. The magnitude of interaction within the recommended dose ranges of either drug is not known.

Hydrocodone: Coadministration of Neurontin® (125 to 500 mg; N=48) decreases hydrocodone (10 mg; N=50) C_{max} and AUC values in a dose-dependent manner relative to administration of hydrocodone alone; C_{max} and AUC values are 3% to 4% lower, respectively, after administration of 125 mg Neurontin® and 21% to 22% lower, respectively, after administration of 500 mg Neurontin®. The mechanism for this interaction is unknown. Hydrocodone increases gabapentin AUC values by 14%. The magnitude of interaction at other doses is not known.

Morphine: A literature article reported that when a 60-mg controlled-release morphine capsule was administered 2 hours prior to a 600-mg Neurontin® capsule (N=12), mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine (see PRECAUTIONS). Morphine pharmacokinetic parameter values were not affected by administration of Neurontin® 2 hours after morphine. The magnitude of interaction at other doses is not known.

Cimetidine: In the presence of cimetidine at 300 mg QID (N=12) the mean apparent oral clearance of gabapentin fell by 14% and creatinine clearance fell by 10%. Thus cimetidine appeared to alter the renal excretion of both gabapentin and creatinine, an endogenous marker of renal function. This small decrease in excretion of gabapentin by cimetidine is not expected to be of clinical importance. The effect of gabapentin on cimetidine was not evaluated.

Oral Contraceptive: Based on AUC and half-life, multiple-dose pharmacokinetic profiles of norethindrone and ethinyl estradiol following administration of tablets containing 2.5 mg of norethindrone acetate and 50 mcg of ethinyl estradiol were similar with and without coadministration of gabapentin (400 mg TID; N=13). The Cmax of norethindrone was 13% higher when it was coadministered with gabapentin; this interaction is not expected to be of clinical importance.

Antacid (Maalox®): Maalox reduced the bioavailability of gabapentin (N=16) by about 20%. This decrease in bioavailability was about 5% when gabapentin was administered 2 hours after Maalox. It is recommended that gabapentin be taken at least 2 hours following Maalox administration.

Effect of Probenecid: Probenecid is a blocker of renal tubular secretion. Gabapentin pharmacokinetic parameters without and with probenecid were comparable. This indicates that gabapentin does not undergo renal tubular secretion by the pathway that is blocked by probenecid.

Drug/Laboratory Tests Interactions

Because false positive readings were reported with the Ames N-Multistix SG® dipstick test for urinary protein when gabapentin was added to other antiepileptic drugs, the more specific sulfosalicylic acid precipitation procedure is recommended to determine the presence of urine protein.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Gabapentin was given in the diet to mice at 200, 600, and 2000 mg/kg/day and to rats at 250, 1000, and 2000 mg/kg/day for 2 years. A statistically significant increase in the incidence of pancreatic acinar cell adenomas and carcinomas was found in male rats receiving the high dose; the no-effect dose for the occurrence of carcinomas was 1000 mg/kg/day. Peak plasma concentrations of gabapentin in rats receiving the high dose of 2000 mg/kg were 10 times higher than plasma concentrations in humans receiving 3600 mg per day, and in rats receiving 1000 mg/kg/day peak plasma concentrations were 6.5 times higher than in humans receiving 3600 mg/day. The pancreatic acinar cell carcinomas did not affect survival, did not metastasize and were not locally invasive. The relevance of this finding to carcinogenic risk in humans is unclear.

Studies designed to investigate the mechanism of gabapentin-induced pancreatic carcinogenesis in rats indicate that gabapentin stimulates DNA synthesis in rat pancreatic acinar cells *in vitro* and, thus, may be acting as a tumor promoter by enhancing mitogenic activity. It is not known whether gabapentin has the ability to increase cell proliferation in other cell types or in other species, including humans.

Gabapentin did not demonstrate mutagenic or genotoxic potential in three *in vitro* and four *in vivo* assays. It was negative in the Ames test and the *in vitro* HGPRT forward mutation assay in Chinese hamster lung cells; it did not produce significant increases in chromosomal aberrations in the *in vitro* Chinese hamster lung cell assay; it was negative in the *in vivo* chromosomal aberration assay and in the *in vivo* micronucleus test in Chinese hamster bone marrow; it was negative in the *in vivo* mouse micronucleus assay; and it did not induce unscheduled DNA synthesis in hepatocytes from rats given gabapentin.

No adverse effects on fertility or reproduction were observed in rats at doses up to 2000 mg/kg (approximately 5 times the maximum recommended human dose on a mg/m^2 basis).

Pregnancy

Pregnancy Category C: Gabapentin has been shown to be fetotoxic in rodents, causing delayed ossification of several bones in the skull, vertebrae, forelimbs, and hindlimbs. These effects occurred when pregnant mice received oral doses of 1000 or 3000 mg/kg/day during the period of organogenesis, or approximately 1 to 4 times the maximum dose of 3600 mg/day given to epileptic patients on a mg/m^2 basis. The no-effect level was 500 mg/kg/day or approximately ½ of the human dose on a mg/m^2 basis.

When rats were dosed prior to and during mating, and throughout gestation, pups from all dose groups (500, 1000 and 2000 mg/kg/day) were affected. These doses are equivalent to less than approximately 1 to 5 times the maximum human dose on a mg/m^2 basis. There was an increased incidence of hydroureter and/or hydronephrosis in rats in a study of fertility and general reproductive performance at 2000 mg/kg/day with no effect at 1000 mg/kg/day, in a teratology study at 1500 mg/kg/day with no effect at 300 mg/kg/day, and in a perinatal and postnatal study at all doses studied (500, 1000 and 2000 mg/kg/day). The doses at which the effects occurred are approximately 1 to 5 times the maximum human dose of 3600 mg/day on a mg/m^2 basis; the no-effect doses were approximately 3 times (Fertility and General Reproductive Performance study) and approximately equal to (Teratogenicity study) the maximum human dose on a mg/m^2 basis. Other than hydroureter and hydronephrosis, the etiologies of which are unclear, the incidence of malformations was not increased compared to controls in offspring of mice, rats, or rabbits given doses up to 50 times (mice), 80 times (rats), and 25 times (rabbits) the human daily dose on a mg/kg basis, or 4 times (mice), 5 times (rats), or 8 times (rabbits) the human daily dose on a mg/m^2 basis.

In a teratology study in rabbits, an increased incidence of postimplantation fetal loss occurred in dams exposed to 60, 300, and 1500 mg/kg/day, or less than approximately ¼ to 8 times the maximum human dose on a mg/m^2 basis. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Nursing Mothers

Gabapentin is secreted into human milk following oral administration. A nursed infant could be exposed to a maximum dose of approximately 1 mg/kg/day of gabapentin. Because the effect on the nursing infant is unknown, Neurontin® should be used in women who are nursing only if the benefits clearly outweigh the risks.

Pediatric Use

Safety and effectiveness of Neurontin® (gabapentin) in the management of postherpetic neuralgia in pediatric patients have not been established.

Effectiveness as adjunctive therapy in the treatment of partial seizures in pediatric patients below the age of 3 years has not been established (see CLINICAL PHARMACOLOGY, Clinical Studies).

Geriatric Use

The total number of patients treated with Neurontin® in controlled clinical trials in patients with postherpetic neuralgia was 336, of which 102 (30%) were 65 to 74 years of

Continued on next page

This product information was prepared in August 2003. On these and other Parke-Davis Products, information may be obtained by addressing PARKE-DAVIS, a Warner-Lambert Division, a Pfizer Company, Morris Plains, New Jersey 07950.

Electronic Orange Book

Approved Drug Products
with
Therapeutic Equivalence Evaluations

Current through October 2007**

** In order to provide timely consumer information on generic drugs, the Electronic Orange Book will be updated daily as new generic approvals occur.
Refer to FAQ for additional information. New!!

Annual Edition

FAQ

Search by Active Ingredient Search by Applicant Holder

Search by Proprietary Name Search by Application Number

Search by Patent

The products in this list have been approved under section 505 of the Federal Food, Drug, and Cosmetic Act.

Drug questions email: DRUGINFO@CDER.FDA.GOV

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Science
Office of Generic Drugs

Electronic Orange Book Query

Search by Active Ingredient:

gabapentin (Type in part or all of name)

Select the list you would like to search:

- (•) Rx (Prescription Drug Products)
- ( ) OTC (Over-the-Counter Drug Products)
- ( ) Disc (Discontinued Drug Products)

Submit Clear

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Active Ingredient Search Results from "OB_Rx" table for query on "gabapentin."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
075350	AB	No	GABAPENTIN	CAPSULE; ORAL	100MG	GABAPENTIN	ACTAVIS ELIZABETH
075350	AB	No	GABAPENTIN	CAPSULE; ORAL	300MG	GABAPENTIN	ACTAVIS ELIZABETH
075350	AB	No	GABAPENTIN	CAPSULE; ORAL	400MG	GABAPENTIN	ACTAVIS ELIZABETH
075360	AB	No	GABAPENTIN	CAPSULE; ORAL	100MG	GABAPENTIN	APOTEX INC
075360	AB	No	GABAPENTIN	CAPSULE; ORAL	300MG	GABAPENTIN	APOTEX INC
075360	AB	No	GABAPENTIN	CAPSULE; ORAL	400MG	GABAPENTIN	APOTEX INC
078150	AB	No	GABAPENTIN	CAPSULE; ORAL	100MG	GABAPENTIN	HIKMA
078150	AB	No	GABAPENTIN	CAPSULE; ORAL	300MG	GABAPENTIN	HIKMA
078150	AB	No	GABAPENTIN	CAPSULE; ORAL	400MG	GABAPENTIN	HIKMA
078428	AB	No	GABAPENTIN	CAPSULE; ORAL	100MG	GABAPENTIN	INTERPHARM
078428	AB	No	GABAPENTIN	CAPSULE; ORAL	300MG	GABAPENTIN	INTERPHARM
078428	AB	No	GABAPENTIN	CAPSULE; ORAL	400MG	GABAPENTIN	INTERPHARM
075477	AB	No	GABAPENTIN	CAPSULE; ORAL	100MG	GABAPENTIN	IVAX PHARMS
075477	AB	No	GABAPENTIN	CAPSULE; ORAL	300MG	GABAPENTIN	IVAX PHARMS
075477	AB	No	GABAPENTIN	CAPSULE; ORAL	400MG	GABAPENTIN	IVAX PHARMS
076537	AB	No	GABAPENTIN	CAPSULE; ORAL	100MG	GABAPENTIN	MUTUAL PHARM
076537	AB	No	GABAPENTIN	CAPSULE; ORAL	300MG	GABAPENTIN	MUTUAL PHARM
076537	AB	No	GABAPENTIN	CAPSULE; ORAL	400MG	GABAPENTIN	MUTUAL PHARM
020235	AB	No	GABAPENTIN	CAPSULE; ORAL	100MG	NEURONTIN	PFIZER PHARMS
020235	AB	No	GABAPENTIN	CAPSULE; ORAL	300MG	NEURONTIN	PFIZER PHARMS

020235 **AB**	Yes	GABAPENTIN	CAPSULE; ORAL	400MG	NEURONTIN	PFIZER PHARMS
076606 **AB**	No	GABAPENTIN	CAPSULE; ORAL	100MG	GABAPENTIN	RANBAXY
076606 **AB**	No	GABAPENTIN	CAPSULE; ORAL	300MG	GABAPENTIN	RANBAXY
076606 **AB**	No	GABAPENTIN	CAPSULE; ORAL	400MG	GABAPENTIN	RANBAXY
075539 **AB**	No	GABAPENTIN	CAPSULE; ORAL	100MG	GABAPENTIN	SANDOZ
075428 **AB**	No	GABAPENTIN	CAPSULE; ORAL	100MG	GABAPENTIN	SANDOZ
075428 **AB**	No	GABAPENTIN	CAPSULE; ORAL	300MG	GABAPENTIN	SANDOZ
075539 **AB**	No	GABAPENTIN	CAPSULE; ORAL	300MG	GABAPENTIN	SANDOZ
075539 **AB**	No	GABAPENTIN	CAPSULE; ORAL	400MG	GABAPENTIN	SANDOZ
075428 **AB**	No	GABAPENTIN	CAPSULE; ORAL	400MG	GABAPENTIN	SANDOZ
077242 **AB**	No	GABAPENTIN	CAPSULE; ORAL	100MG	GABAPENTIN	SUN PHARM INDS LTD
077242 **AB**	No	GABAPENTIN	CAPSULE; ORAL	300MG	GABAPENTIN	SUN PHARM INDS LTD
077242 **AB**	No	GABAPENTIN	CAPSULE; ORAL	400MG	GABAPENTIN	SUN PHARM INDS LTD
075435 **AB**	No	GABAPENTIN	CAPSULE; ORAL	100MG	GABAPENTIN	TEVA PHARMS
075435 **AB**	No	GABAPENTIN	CAPSULE; ORAL	300MG	GABAPENTIN	TEVA PHARMS
075435 **AB**	No	GABAPENTIN	CAPSULE; ORAL	400MG	GABAPENTIN	TEVA PHARMS
075485 **AB**	No	GABAPENTIN	CAPSULE; ORAL	100MG	GABAPENTIN	WATSON LABS
075485 **AB**	No	GABAPENTIN	CAPSULE; ORAL	300MG	GABAPENTIN	WATSON LABS
075485 **AB**	No	GABAPENTIN	CAPSULE; ORAL	400MG	GABAPENTIN	WATSON LABS
021129	Yes	GABAPENTIN	SOLUTION; ORAL	250MG/5ML	NEURONTIN	PARKE DAVIS

Search results from the "OB_Rx" table for query on "020235."

Active Ingredient:	GABAPENTIN
Dosage Form;Route:	CAPSULE; ORAL
Proprietary Name:	NEURONTIN
Applicant:	PFIZER PHARMS
Strength:	100MG
Application Number:	020235
Product Number:	001
Approval Date:	Dec 30, 1993
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	**AB**
Patent and Exclusivity Info for this product:	View

Active Ingredient:	GABAPENTIN
Dosage Form;Route:	CAPSULE; ORAL
Proprietary Name:	NEURONTIN
Applicant:	PFIZER PHARMS
Strength:	300MG
Application Number:	020235
Product Number:	002
Approval Date:	Dec 30, 1993
Reference Lisfed Drug	No
RX/OTC/DISCN:	RX
TE Code:	**AB**
Patent and Exclusivity Info for this product:	View

Active Ingredient:	GABAPENTIN
Dosage Form;Route:	CAPSULE; ORAL
Proprietary Name:	NEURONTIN
Applicant:	PFIZER PHARMS
Strength:	400MG
Application Number:	020235
Product Number:	003
Approval Date:	Dec 30, 1993
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	**AB**
Patent and Exclusivity Info for this product:	View

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Patent and Exclusivity Search Results from query on Appl No 020235 Product 001 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
020235	001	4894476	MAY 02,2008			
020235	001	4894476*PED	NOV 02,2008			
020235	001	6054482	APR 25,2017			
020235	001	6054482*PED	OCT 25,2017			

Exclusivity Data

There is no unexpired exclusivity for this product.

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents submitted on FDA Form 3542 and listed after August 18, 2003 will have one to three patent codes indicating specific patent claims as submitted by the sponsor and are detailed in the above table.
3. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply
4. *PED and PED represent pediatric exclusivity. Patents with pediatric exclusivity granted after August 18, 2003 will be indicated with *PED as was done prior to August 18, 2003. Patents with *PED added after August 18, 2003 will not contain any information relative to the patent itself other than the *PED extension. Information related specifically to the patent will be conveyed on the original patent only.
5. U.S. Patent Nos. RE 36481 and RE 36520 were relisted for Zocor (NDA 19-766) pursuant to the decision and related order in Ranbaxy Labs. v.Leavitt, No. 05-1838 (D.D.C. April 30, 2006). The '481 and '520 patents remained listed in Approved Drug Products with Therapeutic Equivalence Evaluations until any applicable periods of exclusivity pursuant to section 505(j)(5)(B)(iv) of the Federal Food, Drug, and Cosmetic Act were triggered and run. For additional information on this matter, please refer to Docket Nos. 2005P-0008 and 2005P-0046. Patents were subsequently delisted in the December 2006 Orange Book update as the exclusivity periods have triggered and run to expiration.
6. Patent number 4904769 listed on all products of NDA 20482 Precose (Acarbose) was requested to be delisted by the sponsor on 4/16/2007. This patent has remained listed because, under Section 505(j)(5)(D)(i) of the Act, a first applicant may retain eligibility for 180-day exclusivity based on a paragraph IV certification to this patent for a certain period.

View a list of all patent use codes
View a list of all exclusivity codes

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APPENDIX II

THE
MERCK INDEX

AN ENCYCLOPEDIA OF
CHEMICALS, DRUGS, AND BIOLOGICALS

THIRTEENTH EDITION

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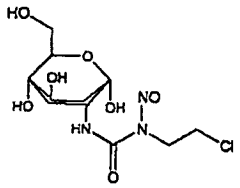
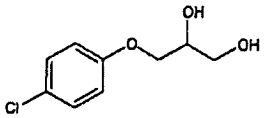


Ivory colored crystals, mp 147-148° (dec with the evolution of gas), (Burns, Heindel). Also reported as mp 140-141° (dec), (Johnston). Sol in water.

Note: This substance is reasonably anticipated to be a human carcinogen: *Ninth Report on Carcinogens* (PB2000-107509, 2000) p III-92.

THERAP CAT: Antineoplastic.

2196. Chlorphenesin. [104-29-0] 3-(4-Chlorophenoxy)-1,2-propanediol; *p*-chlorophenyl α-glyceryl ether; Adermykon; Mycil. $C_9H_{11}ClO_3$; mol wt 202.64. C 53.35%, H 5.47%, Cl 17.50%, O 23.69%. Prepd by condensing equimol amts of *p*-chlorophenol and glycidol in the presence of a tertiary amine or a quaternary ammonium salt as catalyst: Bradley, Forrest, GB 628497 (1949 to British Drug Houses).

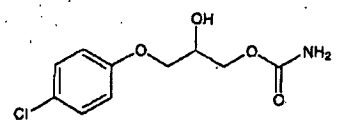


Crystals, mp 77-79°. Soly in water is less than 1%, may be increased by the addition of solubilizers such as ethylurea or propylene glycol: Berger *et al.*, US 2468423 (1949 to British Drug Houses).

THERAP CAT: Antifungal (topical).

2197. Chlorphenesin Carbamate. [886-74-8] 3-(4-Chlorophenoxy)-1,2-propanediol-1-carbamate; carbamic acid 3-(*p*-chlorophenoxy)-2-hydroxypropyl ester; 3-(*p*-chlorophenoxy)-2-hydroxypropyl carbamate; 1,2-propanediol-3-(*p*-chlorophenoxy)-1-carbamate; Maolate; Rinlaxer. $C_{10}H_{12}ClNO_4$; mol wt 245.66. C 48.89%, H 4.92%, Cl 14.43%, N 5.70%, O 26.05%. Prepn: Collins, Matthews, US 3161567; Parker, US 3214336 (1964, 1965 both to Upjohn). Clinical evaluation of analgesic activity: L. J. Cass, W. S. Frederick, *J. New Drugs* **2**, 366 (1962).

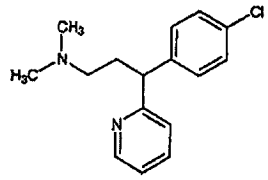
Crystals from benzene + toluene, mp 89-91°. Readily sol in 95% ethanol, acetone, ethyl acetate; fairly readily sol in dioxane. Almost insol in cold water, benzene, cyclohexane. LD_{50} orally in rats: 748 mg/kg; i.v. in mice: 239 mg/kg (Cass, Frederick).



THERAP CAT: Muscle relaxant (skeletal).

THERAP CAT (VET): Muscle relaxant (skeletal).

2198. Chlorpheniramine. [132-22-9] γ-(4-Chlorophenyl)-*N*,*N*-dimethyl-2-pyridinepropanamine; 2-[*p*-chloro-α-(2-dimethylaminoethyl)benzyl]pyridine; 1-(*p*-chlorophenyl)-1-(2-pyridyl)-3-dimethylaminopropane; 1-(*p*-chlorophenyl)-1-(2-pyridyl)-3-*N*,*N*-dimethylpropylamine; 3-(*p*-chlorophenyl)-3-(2-pyridyl)-*N*,*N*-dimethylpropylamine; γ-(4-chlorophenyl)-γ-(2-pyridyl)-propyldimethylamine; chlorprophenpyridamine; chlorphenamine; Haynon. $C_{16}H_{19}ClN_2$; mol wt 274.80. C 69.93%, H 6.97%, Cl 12.90%, N 10.19%. Synthesis: Sperber *et al.*, US 2567245, US 2676964 (1951, 1954, both to Schering). Prepn of *d*-form: L. A. Walter, US 3061517 (1962 to Schering). Solutions: Foley, Ilavsky, US 2766174 (1956 to Schering). Pharmacology: F. E. Roth, W. M. Govier, *J. Pharmacol. Exp. Ther.* **124**, 347 (1958). Toxicity data: R. B. Smith *et al.*, *Toxicol. Appl. Pharmacol.* **28**, 240 (1974). Comprehensive description: C. G. Eckhart, T. McCorkle, *Anal. Profiles Drug Subs.* **7**, 43-80 (1978).



Oily liquid, $bp_{1.0}$ 142°.

Maleate. [113-92-8] Allergisan; Antagonate; Chlor-Trimeton; Chlor-Tripolon; Cloropiril; C-Meton; Histadur; Histaspan; Lorphen; Piriton; Pyridamal-100; Teldrin. $C_{16}H_{19}ClN_2.C_4H_4O_4$; mol wt 390.87. Crystals, mp 130-135°. uv max (water): 261 nm (ε 5760). Soly in mg/ml at 25°: ethanol 330; chloroform 240; water 160; methanol 130. Slightly sol in benzene, ether. pH of a 2% aq soln about 5. LD_{50} orally in mice: 162 mg/kg (Smith).

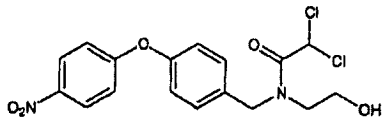
***d*-Form.** [25523-97-1] Dexchlorpheniramine; *d*-chlorpheniramine. Oily liquid. $[\alpha]_D^{25}$ +49.8° (c = 1 in DMF).

***d*-Form maleate.** [2438-32-6] Fortamine; Isomerine; Phenamin; Phendextro; Polamin; Polaramine; Polaronil; Sensidyn. Crystals from ethyl acetate, mp 113-115°. $[\alpha]_D^{25}$ +44.3° (c = 1 in dimethylformamide). pH of 1% soln 4-5.

THERAP CAT: Antihistaminic.

THERAP CAT (VET): Antihistaminic.

2199. Chlorphenoxamide. [3576-64-5] 2,2-Dichloro-*N*-(2-hydroxyethyl)-*N*-[[4-(4-nitrophenoxy)phenyl]methyl]acetamide; *N*-(β-hydroxyethyl)-*N*-[*p*-(4-nitrophenoxy)benzyl]dichloroacetamide; *N*-(β-hydroxyethyl)-*N*-[*p*-phenoxy-(4′-nitro)benzyl]dichloroacetamide; dichloro-*N*-(β-hydroxyethyl)-*N*-[*p*-(4′-nitrophenoxy)benzyl]acetamide; clefamide; chlorophenoxamide; Mebinol. $C_{17}H_{16}Cl_2N_2O_5$; mol wt 399.23. C 51.15%, H 4.04%, Cl 17.76%, N 7.02%, O 20.04%. Prepn: Logemann *et al.*, *Farmaco Ed. Sci.* **13**, 139 (1958); US 2824894 (1958 to Carlo Erba). Antiamebic activity and toxicity data: Carneri, *Giorn. Mal. Infett. Parassit.* **10**, 850 (1958), *C.A.* **53**, 5519C (1959).



Crystals from 95% ethanol, mp 136-137°. Practically insol in water (soly ~3 γ/ml). Sol in ethanol, acetone, dioxane. LD_{50} in mice (mg/kg): >5000 orally, 2000 i.p. (Carneri).

Note: Do not confuse chlorphenoxamide with chlorphenoxamine, *q.v.*

THERAP CAT: Antiamebic.

2200. Chlorphenoxamine. [77-38-3] 2-[1-(4-Chlorophenyl)-1-phenylethoxy]-*N*,*N*-dimethylethanamine; 2-[(*p*-chloro-α-methyl-α-phenylbenzyl)oxy]-*N*,*N*-dimethylethylamine; β-dimethylaminoethyl (*p*-chloro-α-methylbenzhydryl) ether; [1-(*p*-chlorophenyl)-1-phenyl]ethyl (β-dimethylaminoethyl) ether. $C_{18}H_{22}ClNO$; mol wt 303.83. C 71.16%, H 7.30%, Cl 11.67%, N 4.61%, O 5.27%. Prepn: Arnold *et al.*, US 2785202 (1957 to Asta-Werke). Synthesis: G. Cahiez *et al.*, *Tetrahedron Letters* **29**, 3659 (1988). Pharmacology: *eidem*, *Arzneimittel-Forsch.* **4**, 189 (1954); Brock *et al.*, *ibid.* 262. Toxicity studies: Kerley *et al.*, *Toxicol. Appl. Pharmacol.* **4**, 638 (1962). Metab-

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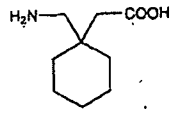
G

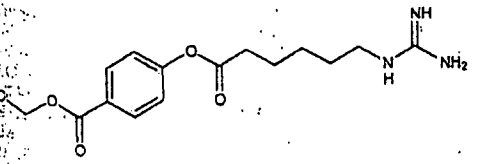
4342. Gabapentin. [60142-96-3] 1-(Aminomethyl)-cyclohexaneacetic acid; CI-945; GS-3450; GOE-3450; Neurontin; $C_9H_{17}NO_2$; mol wt 171.24. C 63.13%, H 10.01%, N 8.18%, O 18.69%. Amino acid structurally related to γ-aminobutyric acid (GABA), *q.v.*, designed to cross the blood brain barrier. Prepn: G. Satzinger *et al.*, DE 2460891 (1976 to Gödecke); *eidem*, US 4024175 (1977 to Warner-Lambert). Pharmacokinetics and metabolism: K.-O. Vollmer *et al.*, *Arzneimittel-Forsch.* 36, 830 (1986). Clinical pharmacology: B. Saletu *et al.*, *Int. J. Clin. Pharmacol. Ther. Toxicol.* 24, 362 (1986). GC determn in biological fluids: W. D. Hooper *et al.*, *J. Chromatog.* 529, 167 (1990). Review of pharmacology and clinical trials in epilepsy: B. Schmidt in *Antiepileptic Drugs*, R. H. Levy *et al.*, Eds. (Raven Press, New York, 3rd ed., 1989) pp 925-935; K. L. Goa, E. M. Sorkin, *Drugs* 46, 409-427 (1993). Clinical trial for treatment of pain in diabetic neuropathy: M. Backonja *et al.*, *J. Am. Med. Assoc.* 280, 1831 (1998). Clinical evaluation in social phobia: A. C. Pande *et al.*, *J. Clin. Psychopharmacol.* 19, 341 (1999).



Crystals from ethanol/ether, mp 162-166° (Satzinger); also reported as mp 165-167° (Schmidt). pKa_1 (25°) 3.68; pKa_2 10.70. Isoelectric point 7.14. Solubility in water at pH 7.4 exceeds 10%.

THERAP CAT: Anticonvulsant.

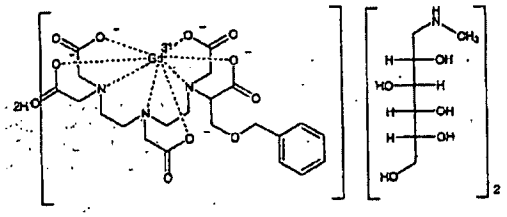
4343. Gabexate. [39492-01-8] 4-[[6-[(Aminoiminomethyl)amino]-1-oxohexyl]oxy]benzoic acid ethyl ester; *p*-hydroxybenzoic acid ethyl ester 6-guanidinohexanoate; *p*-carbethoxyphenyl ε-guanidinocaproate. $C_{16}H_{23}N_3O_4$; mol wt 321.37. C 59.80%, H 7.21%, N 13.08%, O 19.91%. Non-peptide proteolytic enzyme inhibitor which also inhibits the hydrolytic effects of thrombin, plasmin, and kallikrein, trypsin but not chymotrypsin; *cf.* aprotinin. Prepn as the *p*-toluenesulfonate salt: S. Fujii, T. Watanabe, DE 2050484; *eidem*, US 3751447 (1971, 1973 both to Ono). Enzyme inhibition: M. Muramatu, S. Fujii, *Biochim. Biophys. Acta* 268, 221 (1972); S. Tamura *et al.*, *ibid.* 484, 417 (1977). Pharmacology: T. Okegada *et al.*, *Nippon Yakurigaku Zasshi* 71, 71 (1975), *C.A.* 84, 218m (1976). Metabolism: M. Sugiyama *et al.*, *Oyo Yakuri* 9, 733 (1975), *C.A.* 83, 188145s (1975). Metabolism of inhibitory effect on platelet aggregation: G. Kosaki *et al.*, *Thromb. Res.* 20, 587 (1980). Beneficial action in traumatic shock: A. M. Lefer *et al.*, *IRCS Med. Sci.: Libr. Compend.* 8, 278 (1980); in exptl acute pancreatitis: J. R. Wisner *et al.*, *Pancreas* 2, 181 (1987). Comparative clinical study in acute pancreatitis: N. Tanaka *et al.*, *Adv. Exp. Med. Biol.* 120, 367 (1979). Teratology and toxicity study: T. Fujita *et al.*, *Oyo Yakuri* 9, 743 (1975), *C.A.* 83, 188322x (1975).



Methanesulfonate. [56974-61-9] Gabexate mesylate; FOY; Megacert. $C_{16}H_{23}N_3O_4.CH_3SO_3H$; mol wt 417.48. White crystals. Sol in water, ethanol, chloroform. Slightly sol in acetone. Practically insol in ether. pH of soln (1:100): 4.0-5.0. LD_{50} in mice (mg/kg): 8000 orally; 4700 s.c.; 25 i.v. (Fujita).

THERAP CAT: Enzyme inhibitor (proteinase).

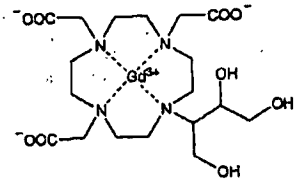
4344. Gadobenate Dimeglumine. [127000-20-8] 1-Deoxy-1-(methylamino)-D-glucitol [4-(carboxy-κO)-5,8,11-tris[(carboxy-κO)methyl]-1-phenyl-2-oxa-5,8,11-triazatridecan-13-oato(5−)-$\kappa N^5,\kappa N^8,\kappa N^{11},\kappa O^{13}$]gadolinate(2−) (2:1); gadolinium benzyloxypropionictetraacetate dimeglumine; Gd-BOPTA/Dimeg; B-19036/7; MultiHance. $C_{36}H_{62}GdN_5O_{21}$; mol wt 1058.28. C 40.85%, H 5.92%, Gd 14.86%, N 6.62%, O 31.75%. $C_{22}H_{26}GdN_3O_{11}.2C_7H_{17}NO_5.2H$. Intravascular paramagnetic MRI contrast agent. Prepn: E. Felder *et al.*, EP 230893; *eidem*, US 4916246 (1987, 1990 both to Bracco); F. Ungeri *et al.*, *Inorg. Chem.* 34, 633 (1995). HPLC determn in biological samples: T. Arbughi *et al.*, *J. Chromatog. B* 713, 415 (1998). Physicochemical properties: C. de Haen *et al.*, *J. Computer Assist. Tomog.* 23, Suppl. 1, S161 (1999). Pharmacology: P. Tirone *et al.*, *ibid.* S195. Pharmacokinetics: V. Lorusso *et al.*, *ibid.* S181. Toxicology: A. Morisetti *et al.*, *ibid.* S207. Clinical study in MRI of liver lesions: J. Petersein *et al.* *Radiology* 215, 727 (2000). Review of clinical studies: B. Hamm *et al.*, *J. Computer Assist. Tomog.* 23, Suppl. 1, S53-S60 (1999).



Hygroscopic powder, mp 124°. Freely sol in water, sol in methanol. Practically insol in *n*-butanol, *n*-octanol, chloroform. Abs max 257.8 nm (*e* 203). $[\alpha]^{20}_{365}$ −26.9° (c = 1.45 in water). Prepd as 0.5*M* soln, osmolality (37°) 1.97 mol/kg. d^{20} 1.22. Viscosity (mPa.s): 9.2 (20°), 5.3 (37°). LD_{50} i.v. in mice (mmol/kg): 5.7 (at 1 mL/min), 7.9 (at 0.2 mL/min); LD_{50} i.v. in rats (mmol/kg): 6.6 (at 6 mL/min), 9.2 (at 1 mL/min) (Morisetti).

THERAP CAT: Diagnostic aid (MRI contrast agent).

4345. Gadobutrol. [138071-82-6] [10-[2,3-Dihydroxy-1-(hydroxymethyl)propyl]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetato(3−)-$N^1,N^4,N^7,N^{10},O^1,O^4,O^7$]gadolinium; Gd-DO3A-butrol; Gadovist. $C_{18}H_{31}GdN_4O_9$; mol wt 604.78. C 35.75%, H 5.18%, Gd 26.00%, N 9.27%, O 23.81%. Neutral, macrocyclic gadolinium chelate. Prepn: J. Platzek *et al.*, EP 448191 (1991 to Schering AG). Physicochemical properties and *in vivo* imaging studies: H. Vogler *et al.*, *Eur. J. Radiol.* 21, 1 (1995). Clinical pharmacokinetics: T. Staks *et al.*, *Invest. Radiol.* 29, 709 (1994). Clinical evaluation of diagnostic use for cerebral metastases: T. J. Vogl *et al.*, *Radiologe* 35, 508 (1995); for glioblastomas: M. Hartmann *et al.*, *Fortschr. Röntgenstr.* 164, 119 (1996).



Hydrophilic. Osmolality (osmol/kg): 0.57 (0.5 mol/l); 1.39 (1 mol/l). Viscosity (cP): 1.43 (0.5 mol/l); 3.7 (1 mol/l). Partition coefficient (butanol/water): 0.006. LD_{50} i.v. in mice: 23 mmol/kg (Vogler).

THERAP CAT: Diagnostic aid (MRI contrast agent).

4346. Gadodiamide. [131410-48-5] [5,8-Bis(carboxymethyl)-11-[2-(methylamino)-2-oxoethyl]-3-oxo-2,5,8,11-tetraazatridecan-13-oato(3−)]gadolinium; gadolinium diethylene-